ORIGINAL

Comparison of clinical course of polymyositis and dermatomyositis : a follow-up study in Tokushima University Hospital

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Abstract : Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting skeletal muscles and other organs, and are associated with high morbidity and mortality rates. In this study, we studied the prevalence, clinical features and its comparative outcome of PM/DM, comparing PM and DM. Twenty-three PM/DM patients (9 PM and 14 DM) were included in this study. The complication of interstitial pneumonia (IP) was found in 17 patients (74%). HRCT showed that non-specific interstitial pneumonia pattern was the most common in patterns of lung involvement. Twenty-one patients (91%) with PM/DM received high dose of prednisolone therapy. The percentage of patients who received methylprednisolone (mPSL) pulse and cyclosporin A was higher in DM patients than in PM patients. The percentage of patients who received mPSL pulse and cyclosporin A was higher in later (after Apr 2004) patients than in former (before Mar 2004) patients. Malignant diseases appeared in 3 patients with DM which consisted of breast cancer, epipharyngeal cancer and gastric cancer. We observed 2 deaths in DM patients during the course of therapy ; one was due to IP, and the other due to miliary tuberculosis. This study showed that a poorer prognosis was observed in patients with DM when compared with those with PM, and immunosuppressive medications may be implicated at least partially in increased risk of infections and malignancies in PM/DM patients especially DM patients, indicating that patients with PM/DM may require careful monitoring during the clinical course. J. Med. Invest. 54 : 295-302, August, 2007

Keywords **:** *polymyositis, dermatomyositis, interstitial pneumonia, prednisolone*

INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory disorders affecting skeletal muscles and other organs (1). PM/DM are associated with high morbidity and mortality rates related to muscle weakness, cardiac and lung involvement (2). Interstitial pneumonia (IP) is one of the most frequent and serious organ involvements in patients with PM/DM (3). The first line of treatment in PM/DM is considered to consist of corticosteroids which continue to be the mainstay of treatment in most pa-

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tients with PM/DM. The use of methylprednisolone (mPSL) pulse can be an effective and rapidly-acting treatment in severe cases (4). When medication of corticosteroids alone is not effective, the use of immunosuppressive agents combined with corticosteroids is selected (5-7). Recent reports have shown that the corticosteroid-resistant IP is successfully treated with cyclosporin A, a T-cell specific immunosuppressant (5, 7). However, the immunosuppressive medications are mainly implicated in high frequency of infections in patients with PM/DM (8).

Recent studies have shown that there are histologic and immunologic differences between PM and DM, suggesting that therapeutic approaches and prognosis may be different. For example, the complication of IP was more frequent in DM patients than in PM patients (6), and the risk of malignant diseases is greater in DM than in PM (10, 11). This study evaluated the prevalence, clinical features and outcome of patients with PM/DM comparing PM and DM.

PATIENTS AND METHODS

Patients

Twenty-three PM/DM patients who had been admitted to our clinical department of Tokushima University Hospital between 2000 and 2006 were included in this study. Diagnosis of PM/DM was made according to the criteria by Bohan and Peter (12, 13) when clinical data fulfilled 4 or 5 of the criteria. Table 1 shows baseline patient characteristics. Patients consisted of 9 PM (2 males and 7 females) aged 54±14 years on average and 14 DM (4 males and 10 females) aged 54±14 years on average. The association of other collagen vascular diseases (CVD) was seen in 2 patients with PM (SLE/SjS/RA, RA) and in a patient with DM (SjS). Anti-Jo1 antibody was positive in 2 patients with PM and a patient with DM. IP was diagnosed just before the initial treatment by a reticulonodular pattern on the chest radiograph and high-resolution computed tomography (HRCT), by decreased PaO_2 levels (less than 80 mmHg) without $PaCO_2$ elevation in arterial blood, and by a restrictive pattern and a decrease in diffusing capacity for carbon monoxide in pulmonary function test. HRCT was available for all patients to investigate radiographic abnormalities. Since HRCT has been shown to be able to suggest the underlying pathologic category (14), the diagnosis of usual interstitial pneumonia (UIP) pattern, non-specific interstitial pneumonia (NSIP) pattern, organizing pneumonia (OP) pattern and diffuse alveolar damage (DAD) pattern was performed based on the HRCT characteristics. The characteristic HRCT features of UIP are predominantly basal and peripheral reticular pattern with honeycombing and traction bronchiectasis. NSIP is characterized by predominantly basal ground-glass opacity and/or reticular pattern, often with traction bronchiectasis. OP is characterized by patchy peripheral or peribronchovascular consolidation. DAD manifests as diffuse lung consolidation and ground-glass opacity. Other clinical data collected from records of patients included regimen of PM/DM therapy.

Table 1. Baseline patient characteristics

	PM	DM
Number of patients	9	14
Sex (M / F)	2 / 7	4 / 10
Average age	54±14	54±14
Other collagen vascular disease	2 (SLE /SjS /RA) (RA)	1 (SjS)
Interstitial pneumonia (+)	5 (56)	12 (86)
Anti-Jo 1 antibody (+)	2 (22)	1 (7)
Elevation of CK	7 (78)	12 (86)
Elevation of CRP	4 (44)	9 (64)
Elevation of KL-6	5 (56)	8 (57)

Parentheses show percentage, Values express as mean±SD.
Ages at the initial treatment were shown.
CK ; creatine kinase, CRP ; c-reactive protein, PM ; polymyositis, DM ; dermatomyositis,
SjS ; Sjogren's syndrome, SLE ; systemic lupus erythematosus, RA ; rheumatoid arthritis

Statistical analysis

All results are expressed as mean±SD. Statistical analyses were performed using Statview software. The results were regarded as significant when p value was <0.05.

RESULTS

Complications

The clinical features and course were compared between patients with PM (Table 2) and DM (Table 3). Muscular symptoms were seen in all patients with PM, and 71% of patients with DM. There was no significant difference between patients with PM (78%) and DM (86%) in % of patients with elevated CK (Table 1). The complication of IP was found in 17 patients (74%) ; 56 % of PM patients and 86% of DM patients (Table 1, 2 and 3). HRCT showed that

Table 2. PM patients

Case No.	Age/sex	Other collagen vascular disease	Interstitial pneumonia	Elevation of CK	Anti-Jo1 antibody	PSL	mPSL	CyA	Prognosis
1	63/F	(−)	UIP	(−)	(+)	(−)	(−)	(−)	Improved (M)
2	61/F	(−)	OP	(−)	(−)	(+)	(−)	(−)	Improved (M, P)
3	54/F	RA	UIP	(+)	(−)	(+)	(−)	(+)	Improved (M, P)
4	57/F	(−)	NSIP	(+)	(−)	(+)	(−)	(+)	Improved (M, P)
5	29/F	SLE, RA, SjS	(−)	(+)	(−)	(+)	(+)	(−)	Improved (M)
6	41/F	(−)	(−)	(+)	(+)	(+)	(−)	(−)	Improved (M)
7	50/M	(−)	(−)	(+)	(−)	(+)	(−)	(−)	Improved (M)
8	69/M	(−)	NSIP	(+)	(−)	(−)	(−)	(−)	Improved (M)
9	58/F	(−)	(−)	(+)	(−)	(+)	(−)	(−)	Improved (M)

PM ; polymyositis, SLE ; systemic lupus erythematosus, RA ; rheumatoid arthritis, SjS ; Sjogren's syndrome, UIP ; usual interstitial pneumonia, OP ; organizing pneumonia, NSIP ; non-specific interstitial pneumonia, PSL ; prednisolone, mPSL ; methylprednisolone, CyA ; cyclosporin A, M ; muscular lesion, P ; pulmonary lesion

Table 3. DM patients

Case No.	Age/sex	Other collagen disease	Interstitial pneumonia	Muscular symptoms	Elevation of CK	Anti-Jo1 antibody	PSL	mPSL	CyA	Prognosis
10	34/F	(−)	NSIP	(+)	(+)	(−)	(+)	(−)	(−)	Improved (M, P)
11	56/F	(−)	NSIP	(−)	(+)	(−)	(+)	(+)	(+)	Improved (M)
12	62/F	(−)	NSIP*	(−)	(+)	(−)	(+)	(+)	(+)	Died
13	48/F	(−)	NSIP	(−)	(−)	(−)	(+)	(+)	(+)	Improved (P)
14	37/F	SjS	NSIP	(+)	(+)	(−)	(+)	(+)	(+)	Improved (M, P)
15	55/F	(−)	UIP	(+)	(+)	(−)	(+)	(−)	(−)	Improved (M, P)
16	70/F	(−)	NSIP	(−)	(−)	(−)	(+)	(−)	(−)	Improved (P)
17	55/F	(−)	OP	(+)	(+)	(+)	(+)	(−)	(+)	Improved (M, P)
18	49/F	(−)	UIP	(+)	(+)	(−)	(+)	(+)	(+)	Improved (M, P)
19	34/M	(−)	NSIP	(+)	(+)	(−)	(+)	(+)	(+)	Improved (M, P)
20	76/M	(−)	(−)	(+)	(+)	(−)	(+)	(−)	(−)	Died
21	67/M	(−)	NSIP	(+)	(+)	(−)	(+)	(−)	(−)	Improved (M, P)
22	64/M	(−)	NSIP	(+)	(+)	(−)	(+)	(−)	(+)	Improved (M, P)
23	67/F	(−)	(−)	(+)	(+)	(−)	(+)	(−)	(−)	Improved (M)

DM ; dermatomyositis, SjS ; Sjogren's syndrome, NSIP ; non-specific interstitial pneumonia, DAD ; diffuse alveolar damage, UIP ; usual interstitial pneumonia, OP ; organizing pneumonia, CK ; creatine kinase, PSL ; prednisolone, mPSL ; methylprednisolone, CyA ; cyclosporin A, M ; muscular lesion, P ; pulmonory lesion
*NSIP pattern changed into DAD pattern in clinical course.

UIP pattern was found in 4 patients, NSIP pattern in 11 patients, and OP pattern in 2 patients (Table 4). DAD pattern appeared in a patient with DM who had originally showed NSIP pattern (Case 12). The level of KL-6 before the therapy was higher in patients with UIP pattern than in patients with NSIP pattern though there was no significant difference. The presence of anti-Jo1 antibody has been shown to be highly associated with IP in PM/DM patients (3), but this study failed to demonstrate the interaction of the presence of IP and anti-Jo1 antibody because of the limited number of patients we enrolled and a few frequency of positive anti-Jo1 antibody in our patients. PM/DM frequently occurs in overlap with CVD (1). In our cases, the association of other CVD was seen in 2 patients with PM (SLE/SjS/RA, RA) and in a patient with DM (SjS).

Treatment

Twenty-one patients (91%) with PM/DM received high dose of corticosteroids using prednisolone (Table 2, 3 and 5). High dose prednisolone therapy was performed in 7 PM patients (78%) and in all of DM patients. Ten patients (42%) with PM/DM received cyclosporin A. More patients were treated with cyclosporin A in DM patients (57%) than in PM patients (22%). Muscular lesions were improved by the therapy in all of PM/DM patients

Table 4. Clinical findings of interstitial pneumonia

Interstitial pneumonia	Classified in HRCT	Number of patients	PM/DM	KL-6 (U/ml)	Muscular symptoms (+)	Elevation of CK (+)	Combination	
							mPSL pulse	CyA
−		6	4/2	226±54	6 (100)	6 (100)	1 (17)	0 (0)
+	UIP pattern	4	2/2	2384±3072	4 (100)	3 (75)	1 (25)	1 (25)
	NSIP pattern	11*	2/9	620±231	7 (64)	9 (82)	5 (45)	8 (73)
	DAD pattern	0*						
	OP pattern	2	1/1	1650±1429	2 (100)	1 (50)	0 (0)	1 (50)

Parentheses show percentage, Values express as mean ± SD.
UIP ; usual interstitial pneumonia, NSIP ; non-specific interstitial pneumonia, DAD ; diffuse alveolar damage, OP ; organizing pneumonia, CK ; creatine kinase, mPSL ; methylprednisolone, CyA ; cyclosporin A
*NSIP pattern in a patient changed into DAD pattern in clinical course.

Table 5. Treatment

	Number of patients	Sex (M/F)	Age	%PM	Muscular improvement		Pulmonary improvement	
					Muscular symptoms	CK	HRCT	KL-6
prednisolone alone	11	3/8	55±16	45	10 (100)	9 (100)	5 (100)	2 (67)
prednisolone + cyclosporin A (at the same time)	4	0/4	51±11	0	2 (100)	3 (100)	3 (75)	3 (100)
prednisolne + cyclosporin A (on the way)	6	2/4	52±10	33	5 (100)	6 (100)	5 (83)	3 (60)

Parentheses show percentage, Values express as mean ± SD.
%PM =(the number of PM patients/the number of total patients) ×100, CK ; creatine kinase, HRCT ; high-resolution computed tomography

Table 6. Comparison of clinical course between patients with and without methylprednisolone pulse therapy

mPSL pulse therapy	Number of patients	%PM	Age	Sex (M/F)	Muscular improvement		pulmonary improvement		Complications		
					Muscular symptoms	CK	HRCT	KL-6	Diabetes	Serious complication	Aseptic necrosis of the femoral head
+	7	14	45±12	1/6	4 (100)	6 (100)	4 (67)	3 (50)	1 (14)	2 (29)	1 (14)
−	16	50	59±11*	4/12	15 (100)	13 (100)	9 (100)	5 (56)	4** (25)	5 (31)	0 (0)

Parentheses show percentage, Values express as mean ± SD.
%PM =(the number of PM patients/ the number of total patients) ×100,
mPSL ; methylprednisolone, CK ; creatine kinase, HRCT ; high-resolution computed tomography
* p=0.04, ** A patient was complicated before the treatment.

who had them before the treatment. HRCT findings showed that the improvement of IP was observed in 13 patients (76%) of 17 PM/DM patients with IP ; 60 % of PM patients and 83% of DM patients. Seven (29%) of patients with PM/DM were treated with mPSL pulse as an initial therapy (Table 6). The percentage of PM patients was lower in patients treated with mPSL pulse (14%) than in those without mPSL pulse (50%). Patients who were treated with mPSL pulse were significantly younger than those without mPSL pulse. There was no difference in the complication of diabetes mellitus, severe infections, or aseptic necrosis of the femoral head after the therapy between patients treated with mPSL

pulse and those without mPSL pulse.

Comparison of selection of therapeutic drugs between former and later times

The selection of therapeutic drugs is compared between patients in former (Aug 2000-May 2004) and later (Apr 2004-Oct 2006) times (Table 7). There was no difference in the percentage of PM patients between these two times. The percentage of patients who received cyclosporin A was higher in later times (58%) than in former times (27%). Patients who received mPSL pulse therapy were also increased in later times (42%) when compared with former times (18%).

Adverse events and prognosis

Malignant diseases appeared in 3 patients with DM which consisted of breast cancer, epipharyngeal cancer and gastric cancer (Table 8). Patients with breast cancer and gastric caner received surgical resection of the lesion successfully. The patient with epipharyngeal cancer received the combination therapy with chemotherapy and radiation, and then was followed in another hospital. The lesion of DM such as myositis and IP did not change during the therapy for cancer. No malignant disease was observed in patients with PM. Six patients experienced severe infections ; a pneumocystis pneunonia, 3 bacterial pneumonia, a fungus infection and a miliary tuberculosis. A mean duration between onset of the infections and the treatment is 15±19 months. We observed 2 deaths during the course. There is a death due to IP by developing DAD pattern, and a death due to miliary tuberculosis. Recurrence was observed in 3 patients. The recurrence of IP was observed in a patient with PM when the dose of prednisolone was decreased to 7.5 mg/day, and that of myositis was in 2 patients with DM when prednisolone was decreased to 7 and 9 mg/day, respectively (data not shown).

Table 7. Comparison of clinical course between former and later times

	Number of patients	Sex (M/F)	Age	PM/DM	PSL + CyA	mPSL pulse	Muscular improvement		pulmonary improvement	
							Muscular symptoms	CK	HRCT	KL-6
Aug 2000 ~ Mar 2004	11	5/6	59±12	5/6	3 (27)	2 (18)	9 (100)	7 (100)	6 (67)	4 (50)
Apr 2004 ~ Oct 2006	12	1/11	51±13	4/8	7 (58)	5 (42)	10 (100)	12 (100)	7 (88)	4 (80)

Parentheses show percentage, Values express as mean ± SD.
PM ; polymyositis, DM ; dermatomyositis, CyA ; cyclosporin A, PSL ; prednisolone, mPSL ; methylprednisolone
CK ; creatine kinase, HRCT ; high-resolution computed tomography

Table 8. Serious complications

Case No.	Complications	mPSL pulse	prednisolone		CyA	Period (months)*
			The starting dose (mg/day)	The dose at onset (mg/day)		
Case 2	Pneumocystis pneumonia	(−)	50	40	(−)	2
Case 3	Bacterial pneumonia	(−)	50	5	(−)	49
Case 11	Breast cancer	(+)	60	10	(+)	20
	Aspergillosis			50		2
	Nocardiosis			45		3
	Fungal endophthalmitis			40		3
Case 15	Bacterial pneumonia	(−)	40	10	(−)	29
Case 20	Miliary tuberculosis	(−)	100	35	(−)	1
Case 21	Upper pharyngal cancer	(−)	60	60	(−)	1
	Bacterial pneumonia			5		33
Case 23	Gastric cancer	(−)	20	3	(−)	12

period between initial treatment and appearance of complication.
mPSL ; methylprednisolone, CyA ; cyclosporin A

DISCUSSION

In this study, clinical course of PM/DM in our clinical department was studied comparing PM and DM. Our study showed that 74% of patients with PM/DM experienced IP, and its complication was more frequent in DM patients than in PM patients. The prevalence of IP in PM/DM has been reported to vary between 23% and 65% (3, 7) depending on criteria applied. The following two reasons are considered for high incidence of IP in PM/DM patients in our study. First, chest HRCT which was known to be a sensitive test to diagnose IP was performed in all of patients with PM/DM in our study. Second, PM/DM patients with IP were transferred from other clinics to our hospital because our laboratory has majored in respiratory diseases. IP is one of the most frequent and serious organ involvements in patients with PM/DM. Arsura and Greenberg have shown a decreased survival in patients with IP compared with those without IP (60% at 31 months versus 76% at 60 months) (15). In this study, however, 13 patients (76%) of PM/DM patients experienced improvement of IP ; 60% of PM patients and 83% of DM patients, and the prognosis for IP was in good course during follow-up periods. HRCT demonstrated that most (65%) of patients with IP showed NSIP pattern and less patients (24%) did UIP pattern. Since it has been reported that patients with UIP have poorer course in comparison with those with NSIP (16), a better prognosis of PM/DM patients observed in this study might be due to high frequency of NSIP. On the other hand, previous reports showed that the survival of PM-IP patients was better than that of DM-IP (7). It has been also shown that 44-60% of IP in PM/DM, especially DM, is resistant to high-dose corticosteroid therapy and the corticosteroid-resistant IP patients died of respiratory failure in a relatively short period (3). However, in this study there was no difference in morbidity and mortality due to IP between PM and DM though there was a patient with DM who died of DAD changed from NSIP. The reason for the discrepancy between our study and previous reports is not clear, but it may be explained by high percentages of NSIP in DM patients in this study.

The first line of treatment in PM/DM consists of corticosteroids. Recently, however, favorable outcome with immunosuppressive therapy in patients with PM/DM has been reported (5, 7, 17). Of the immunosuppressive agents, cyclosporin A has been shown to prolong survival of patients with PM/DM (5, 7, 17, 18). Cyclosporin A forms a complex with an intracytoplasmic protein, cyclophilin, and this complex inhibits the intracellular phosphatase calcineurin resulting in the inhibition of interleukin-2 release from helper T cells. This inhibition suppresses both proliferation and function of CD4+ T cells. In this study, cyclosporin A was used as combination with prednisolone in 10 PM/DM patients (48%). Cyclosporin A was started in 4 patients at the same time as prednisolone, and was started in 6 patients on the way of the course when disease activity remained after the treatment with prednisolone alone. The percentage of patients who received the treatment with cyclosporin A was more in later times (after Apr, 2004) when compared with in former times (before Mar, 2004) which resulted from increased evidence about efficacy in cyclosporin A in PM/DM. The percentage of patients who received mPSL pulse was also increased in later times when compared in former times. The treatment with mPSL pulse is increasing being used in patients with acute and severe disease activities of PM/DM such as active IP, and the early use of mPSL pulse is considered to be useful to control them (4). However, whether mPSL pulse therapy results in more rapid control of disease activity or lower cumulative doses of prednisolone has not been determined.

In this study, 2 DM patients died during the course ; one patient died of developing DAD, and the other died of miliary tuberculosis. Previous reports showed that IP is a major cause of death in patients with PM/DM and contributes substantially to morbidity and mortality especially in DM (19-21). On the other hand, high frequency of infectious complications has been shown in patients with PM/DM (2, 22) with significant morbidity and mortality. In PM/DM, infectious complications have been described in up to 26% of patients (8). In this study, patients with PM/DM experienced 8 severe infectious events in 6 cases (26%). Most common events were bacterial pneumonia and fungal infections. These infections occurred at 1-49 months after the initial treatment at dose of 5-50 mg/day of prednisolone. Of them, a case died of miliary tuberculosis, but others were healed by the treatment. Although several factors may be implicated in increased frequency of infections in PM/DM patients, the treatment with immunosuppressive medications may be one of major factors. Marie, *et al.* showed that risk factors for opportunistic infections are the use of immunosuppressive drugs, lymphopenia, and lower serum total protein levels, and mortality rates by

infections were as high as 27.7% in PM/DM patients with opportunistic infections (8). This study showed that cyclosporin A and mPSL pulse were used in more patients in later times in our hospital which suggested the possibility of serious opportunistic infection might be increased during the therapeutic course. Therefore, our results suggest that patients with PM/DM presenting with factors predictive of opportunistic infection may require closer monitoring.

Three patients had malignant diseases which consisted of breast cancer, epipharyngeal cancer and gastric cancer. All patients had DM, and were older than 56 y.o.. Recent reports strongly support an increased risk of malignant diseases in patients with DM, and older patients with DM are at greater risk (10, 11, 23, 24). Hill, *et al.* reported that 198 (32%) of 618 cases with DM had cancer, and of these, 115 (59%) developed a malignant disease after the diagnosis of DM (10). On the other hand, 137 (15%) of 914 cases with PM had cancer, which developed after diagnosis of PM in 95 (69%) (10). Similarly, Airio, *et al.* showed that the relative risk of cancer among DM patients but not PM patients was high, and the risk was high among patients with DM older than 49 (11). DM patients was strongly associated with ovarian, lung, pancreatic, stomach and colorectal cencer, and non-Hodgkin lymphoma, and the overall risk of cancer was greatest in the first 3 years after the diagnosis, but a greater risk of malignancy persists through all years of follow-up. (24). These data suggest that a cancer evaluation of PM/DM patients, especially DM patients, is important at the initial diagnosis, and one needs to follow the patient carefully for a number of years.

In conclusion, we have shown clinical series of patients with PM/DM in our clinical department. Higher frequency in complications of malignancies and opportunistic infections was observed in patients with DM than those with PM. All of patients who died during the course were patients with DM. Immunosuppressive medications may be implicated at least partially in increased risk of infections and malignancies in PM/DM patients especially DM patients. This study indicates that patients with PM/DM may require careful monitoring in clinical course.

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